EFSA Panel on Dietetic Products, Nutrition and Allergies; Scientific Opinion on the substantiation of a health claim related to collagen hydrolysate and maintenance of joints pursuant to Article 13(5) of Regulation (EC) No 1924/2006

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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to collagen hydrolysate and maintenance of joints pursuant to Article 13(5) of Regulation (EC) No 1924/2006[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following an application from Gelita AG, submitted via the Competent Authority of Germany, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of a health claim related to collagen hydrolysate and maintenance of joint health. The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence and including a request for the protection of proprietary data. The food constituent that is the subject of the health claim is collagen hydrolysate. The Panel considers that the collagen hydrolysate is sufficiently characterised. The claimed effect is "maintenance of joint health". The target population as proposed by the applicant is physically active people. The Panel considers that the maintenance of joints is a beneficial physiological effect. The applicant provided one narrative review, three intervention studies in humans, one animal study, two *in vitro* studies, and two bioavailability studies as pertinent to the claim. The narrative review did not contain any primary data which were pertinent to the claim. One of the human studies was conducted in patients while another study was not controlled and no scientific conclusions could be drawn from these studies for the substantiation of the claimed effect. One trial in 147 active student athletes evaluated a total of 15 parameters related to joint pain/discomfort. There were no significant differences between groups for any endpoint when significance levels were adjusted for multiple comparisons. In weighing the evidence, the Panel took into account that one study in physically active humans did not show an effect of collagen hydrolysate on joint discomfort, and that studies in animals and *in vitro* do not predict an effect of collagen hydrolysate on maintenance of joints in humans *in vivo*. The Panel concludes that a cause and effect relationship has not been established between the consumption of collagen hydrolysate and maintenance of joints.

KEY WORDS

Collagen, joints, health claims

[1] On request from the Competent Authority of Germany following an application by Gelita AG, Question No EFSA-Q-2011-00201, adopted on 30 June 2011.

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SUMMARY

Following an application from Gelita AG, submitted pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Germany, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of a health claim related to collagen hydrolysate and maintenance of joint health.

The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence and including a request for the protection of proprietary data.

The food constituent that is the subject of the health claim is collagen hydrolysate. Complete specifications such as flow chart of the manufacturing process, the typical amino acid profile of the hydrolysate, and stability information have been provided. The Panel considers that the collagen hydrolysate, which is the subject of the health claim, is sufficiently characterised.

The claimed effect is "maintenance of joint health". The target population, as proposed by the applicant, is physically active people. The Panel considers that the maintenance of joints is a beneficial physiological effect.

The applicant provided one narrative review, three intervention studies in humans, one animal study, two *in vitro* studies, and two bioavailability studies as pertinent to the claim.

The narrative review on collagen hydrolysate for treatment of osteoarthritis and other joint disorders did not contain any primary data which were pertinent to the claim.

One of the human studies on the effects of collagen hydrolysate on the composition of hyaline cartilage was conducted in patients with knee osteoarthritis. The Panel considers that the evidence provided does not establish that patients with osteoarthritis are representative of the target population with regard to the status of joint tissues, or that results obtained in studies on subjects with osteoarthritis relating to effects on the composition of cartilage can be extrapolated to the target population (physically active people without osteoarthritis). No scientific conclusions can be drawn from this study for the substantiation of the claimed effect.

One intervention study with 100 healthy athletes was an open label non-controlled trial. The Panel considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

In a randomised, double-blind, placebo-controlled trial, 147 active student athletes who complained about physical activity-related joint discomfort because of joint stress, injury, surgical outcome, or trauma, received 10 g collagen hydrolysate per day or placebo for 24 weeks. Subjects were randomly assigned to two groups: a group receiving collagen hydrolysate and a group receiving a placebo which contained xanthan. Joint discomfort was recorded at baseline and at 6, 12, 18 and 24 weeks using a visual analogue scale (VAS). A physician rated the following parameters: joint pain at rest, joint pain related to exertion, restricted ability to move, and state of inflammation. Study subjects rated their subjective symptoms using the same VAS: pain when walking, standing, running a straight line, running and changing direction, carrying objects, lifting, extending arms, rotating the shoulder, reaching, throwing, and at rest. The primary end-points of the study (a total of 15) were defined as the baseline adjusted VAS scores after 24 weeks of treatment. Of the 147 subjects recruited, 97 were included in the statistical analysis. The Panel notes that the statistical analysis did not include imputation of the missing data. The Panel also notes that the statistical model did not use all the observed data (i.e. data from all of the visits). All study participants improved, i.e. all experienced decreased pain, during the study. However, there were no significant differences between groups for any endpoint when significance levels were adjusted for multiple comparisons according to Bonferroni-Holm.

One animal study was carried out in a mouse model of osteoarthritis and investigated an effect of orally administered collagen hydrolysate on the development and the progression of osteoarthritis. The Panel considers that the evidence provided does not establish that an effect of collagen hydrolysate on joints in this mouse model can predict an effect on maintenance of joints in humans.

In vitro studies were provided on the effect of collagen hydrolysate on the metabolism of chondrocyte extracellular matrix. The Panel considers that the evidence provided does not establish that effects of collagen hydrolysate on the metabolism of chondrocyte extracellular matrix *in vitro* predict an effect *in vivo*.

The Panel considers that the bioavailability studies do not provide evidence for a mechanism for the proposed effect of collagen hydrolysate on joints.

In weighing the evidence, the Panel took into account that one study in physically active humans did not show an effect of collagen hydrolysate on joint discomfort, and that studies in animals and *in vitro* do not predict an effect of collagen hydrolysate on maintenance of joints in humans *in vivo.*

The Panel concludes that a cause and effect relationship has not been established between the consumption of collagen hydrolysate and maintenance of joints.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

Regulation (EC) No 1924/20064 harmonises the provisions that relate to nutrition and health claims, and establishes rules governing the Community authorisation of health claims made on foods. As a rule, health claims are prohibited unless they comply with the general and specific requirements of this Regulation, are authorised in accordance with this Regulation and are included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Article 13(5) of this Regulation lays down provisions for the addition of claims (other than those referring to the reduction of disease risk and to children's development and health) which are based on newly developed scientific evidence, or which include a request for the protection of proprietary data, to the Community list of permitted claims referred to in Article 13(3).

According to Article 18 of this Regulation, an application for authorisation or inclusion in the Community list of permitted claims referred to in Art 13(3) shall be submitted by the applicant to the national competent authority of a Member State, which will make the application and any supplementary information supplied by the applicant available to the European Food Safety Authority (EFSA).

STEPS TAKEN BY EFSA:

- The application was received on 11/03/2011.
- The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence and including a request for the protection of proprietary data.
- On 04/04/2011, during the validation process of the application, EFSA sent a request to the applicant to provide missing information.
- The applicant provided the missing information on 02/05/2011.
- The scientific evaluation procedure started on 10/05/2011.
- On 13/05/2011, the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application and on 24/05/2011 EFSA requested the applicant to provide this additional information.
- The applicant submitted the requested information on 08/06/2011.
- During the meeting on 30/06/2011, the NDA Panel, having evaluated the data submitted, adopted an opinion on the scientific substantiation of a health claim related to collagen hydrolysate and maintenance of joints.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16(3) of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an opinion on the scientific substantiation of a health claim related to: collagen hydrolysate and maintenance of joints.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of collagen hydrolysate, a positive assessment of its safety, nor a decision on whether collagen

[4] European Parliament and Council (2006). Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. Official Journal of the European Union OJ L 404, 30.12.2006. Corrigendum OJ L 12, 18.1.2007, p. 3–18.

hydrolysate is, or is not, classified as a foodstuff. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

It should also be highlighted that the scope, the proposed wording of the claim, and the conditions of use as proposed by the applicant may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 18(4) of Regulation (EC) No 1924/2006.

INFORMATION PROVIDED BY THE APPLICANT

Applicant's name and address: Gelita AG, Uferstrasse 7, 69412 Eberbach, Germany.

The application includes a request for the protection of proprietary data in accordance with Article 21 of Regulation (EC) No 1924/2006. In particular, the applicant claimed proprietary rights for two of the studies provided for the substantiation of the claim (Clark et al., 2008; Flechsenhar and Alf, 2005).

Food/constituent as stated by the applicant

According to the applicant, a characteristic mixture of collagen peptides derived from hydrolysis of predominantly bovine or porcine type I and type III collagen.

Health relationship as claimed by the applicant

According to the applicant, maintenance of joint health.

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the claim: "Characteristic collagen peptide mixture (collagen hydrolysate) having a beneficial physiological effect on the maintenance of joint health in physically active people."

Specific conditions of use as proposed by the applicant

The applicant has proposed an intake of 10 g collagen hydrolysate per day. The target population is physically active people.

ASSESSMENT

1. Characterisation of the food/constituent

The food constituent that is the subject of the health claim is collagen hydrolysate.

The raw material for the production process is bovine and porcine skins. Complete specifications such as flow chart of the manufacturing process, the typical amino acid profile of the hydrolysate, and stability information have been provided.

The Panel considers that the food constituent, collagen hydrolysate, which is the subject of the health claim, is sufficiently characterised.

2. Relevance of the claimed effect to human health

The claimed effect is "maintenance of joint health". The target population, as proposed by the applicant, is physically active people.

For claims on maintenance of joints, possible outcomes related to joint structure and function include, for example, joint space width, mobility, stiffness and (dis)comfort (e.g. pain).

The Panel considers that the maintenance of joints is a beneficial physiological effect.

3. Scientific substantiation of the claimed effect

The applicant performed a literature search in PubMed and Google, using the search terms "collagen hydrolysate" in combination with "cartilage", "joint health", and "clinical trial". Inclusion criteria included clinical studies on healthy individuals and experimental studies in osteoarthritis patients, in mice, in cartilage cells and in cartilage tissue explants, all performed with the specific collagen hydrolysate described in section 1; additional clinical and animal studies on collagen hydrolysate related to the bioavailability of collagen hydrolysate were included.

The applicant provided one narrative review, three intervention studies in humans, one animal study and two *in vitro* studies, all performed with the collagen hydrolysate as specified in section 1, and two bioavailability studies (one in humans and one in animals) with collagen hydrolysates different from the one specified in section 1, as pertinent to the claim.

A narrative review on collagen hydrolysate for treatment of osteoarthritis and other joint disorders (Bello and Oesser, 2006) did not contain any primary data which were pertinent to the claim.

One of the human studies on the effects of collagen hydrolysate on the composition of hyaline cartilage was conducted in patients with knee osteoarthritis (McAlindon et al., 2009). The Panel considers that the evidence provided does not establish that patients with osteoarthritis are representative of the target population with regard to the status of joint tissues, or that results obtained in studies on subjects with osteoarthritis relating to effects on the composition of cartilage can be extrapolated to the target population (physically active people without osteoarthritis). The available scientific evidence indicates that normal cells and tissues are genetically and functionally different from osteoarthritic cells and tissues and therefore may respond differently to intervention with exogenous substances (FDA, 2004). No scientific conclusions can be drawn from this study for the substantiation of the claimed effect.

In an open label non-controlled intervention study 100 healthy athletes, aged 15-80 years and who were complaining of joint pain in the hip, knee or shoulder owing to physical activity, received 10 g collagen hydrolysate per day for 12 weeks (Flechsenhar and Alf, 2005). The study recorded restricted ability to move, pain related exertion, pain when walking up the stairs, and pain when manipulating objects with one's hands above the head. The Panel notes that this study was not controlled. The Panel considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

In a randomised, double-blind, placebo-controlled trial, 147 (72 male, 75 female) active student athletes, mean age 20 years and who complained about physical activity-related joint discomfort because of joint stress, injury, surgical outcome, or trauma, received 10 g collagen hydrolysate per day or placebo for 24 weeks (Clark et al., 2008; Gelita AG, 2007, unpublished). Potential subjects were excluded if they had an acute injury of a joint or an inflammatory process, ingested glucosamine, chondroitin, or other nutritional supplements indicated for treatment of joint pain and osteoarthritis or who, from a clinical perspective, were considered likely to increase their dose of analgesic medication during the 24-week study because of severe arthralgia.

Subjects were randomly assigned to two groups: a group (n=73) receiving 25 mL of a liquid formulation which contained 10 g of collagen hydrolysate and a group (n=74) receiving a placebo, which consisted of 25 mL of liquid containing xanthan. During the trial, subjects were permitted to continue taking their regular analgesics or nonsteroidal anti-inflammatory drugs.

Joint discomfort was recorded at baseline and at 6, 12, 18 and 24 weeks using a visual analogue scale (VAS) divided in increments of 1 to 10 for severity of symptoms, with 1 = no symptoms and 10 = very severe symptoms. The physician rated the following parameters based on a physical examination and taking available clinical data into account: joint pain at rest, joint pain related to exertion, restricted ability to move, and state of inflammation. Study subjects rated their subjective symptoms

using the same VAS: pain when walking, standing, running a straight line, running and changing direction, carrying objects, lifting, extending arms, rotating the shoulder, reaching, throwing, and at rest. The first five were rated when lower joints were affected and the others when upper extremities were affected. The primary end-points of the study (a total of 15) were defined as the baseline adjusted VAS scores after 24 weeks of treatment. No power calculations were provided but the authors indicated that 150 subjects divided into two treatment groups was estimated to be sufficient to show significant results for joint pain based on experience gained in the observational study of Flechsenhar and Alf (2005).

Use of medications (pain relievers, anti-inflammatory agents, cyclo-oxygenase inhibitors, and other over the counter analgesics) and alternative therapies were recorded at baseline and at 6, 12, 18 and 24 weeks. The Panel notes that the possible effects of medication on assessment of severity of symptoms were not taken into account (e.g. no washout of medication before assessment).

Of the 147 subjects recruited, 97 were included in the statistical analysis, 46 (23 female) in the collagen hydrolysate group and 51 (29 female) in the placebo group. Of the 50 subjects excluded, 10 were considered ineligible at the first visit, 17 did not present for the first visit, eight were excluded because of faulty documentation during the first visit, four suffered an adverse event, and 11 presented fewer than three times. For statistical analysis, multiple testing was performed by adapting the significance levels according to Bonferroni-Holm. The Panel notes that the statistical analysis did not include imputation of the missing data. The Panel also notes that the statistical model did not use all of the observed data (i.e. data from all the visits).

A number of secondary end-points were measured, e.g. intake of medication (anti-inflammatory drugs, COX-2 inhibitors, and other pain relievers) and use of alternative therapies. However, the authors considered that no conclusions could be drawn from a comparison between groups for these outcomes as the statistical analysis did not include adjustment for multiple comparisons.

Baseline comparison showed the groups to be similar for the 15 end-points except for physician rated 'restricted ability to move' (less severe for collagen hydrolysate group) and self rated 'joint pain rotating the shoulder' (less severe for collagen hydrolysate group). There were no significant differences between groups for duration or cause of pain (e.g. degenerative disease, sports injury, joint deformation, or genetic predisposition), or numbers of subjects taking medications (anti-inflammatory drugs, COX-2 inhibitors, and other pain relievers) - 15 out of 44 collagen hydrolysate patients, and 17 of the 49 placebo patients reported taking some form of medication.

All study participants improved, i.e. all experienced decreased pain, during the study. However, there were no significant differences between groups for any end point when significance levels were adjusted for multiple comparisons according to Bonferroni-Holm (Gelita AG, 2007, unpublished).

A subgroup analysis of subjects with knee arthralgia (n=63) was performed. The Panel notes that this comparison was not pre-planned in the study protocol and that no scientific justification has been provided for it. The Panel considers that no conclusions can be drawn from this sub-group analysis for the scientific substantiation of the claim.

The Panel considers that this study does not show an effect of collagen hydrolysate consumption on joint discomfort.

In a mouse model of osteoarthritis (an inbred mouse strain which spontaneously develops osteoarthritic lesions) collagen hydrolysate, or placebo (bovine serum albumin), was orally administered once daily at a dosage of 0.15 mg/g body weight from age 2 to 6 months to investigate an effect on development of osteoarthritis or from age 6 to 8 months to investigate an effect on progression of osteoarthritis (Collagen Research Institute, 2011, unpublished). The Panel considers

that the evidence provided does not establish that an effect of collagen hydrolysate on joints in this mouse model can predict an effect on maintenance of joints in humans.

In vitro studies were provided on the effect of collagen hydrolysate on the metabolism of chondrocyte extracellular matrix (Oesser and Seiffert, 2003; Oesser and Seiffert, 2005; Schunk and Oesser, 2011). The Panel considers that the evidence provided does not establish that effects of collagen hydrolysate on the metabolism of chondrocyte extracellular matrix *in vitro* can predict an effect on the maintenance of joints in humans *in vivo*.

A study was provided on the digestion and absorption of porcine type I collagen hydrolysate in humans. The study showed that free hydroxyproline (Hyp) as well as Hyp-dipeptides (e.g. Pro-Hyp) and tripeptides were detected in plasma after ingestion of collagen hydrolysate (Iwai et al., 2005). A study on the absorption and tissue distribution of ^{14}C labelled rat type I (predominantly) collagen hydrolysate fed intragastrically to mice compared to ^{14}C labelled proline fed with unlabelled collagen hydrolysate showed preferential uptake of ^{14}C into cartilage from the ^{14}C labelled collagen hydrolysate (Oesser et al., 1999). The Panel considers that these studies do not provide evidence for a mechanism for the proposed effect of collagen hydrolysate on joints.

In weighing the evidence, the Panel took into account that one study in physically active humans did not show an effect of collagen hydrolysate on joint discomfort, and that studies in animals and *in vitro* do not predict an effect of collagen hydrolysate on maintenance of joints in humans *in vivo.*

The Panel concludes that a cause and effect relationship has not been established between the consumption of collagen hydrolysate and maintenance of joints.

CONCLUSIONS

On the basis of the data presented, the Panel concludes that:

- The food constituent, collagen hydrolysate, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect is “maintenance of joint health”. The target population, as proposed by the applicant, is physically active people. Maintenance of joints is a beneficial physiological effect.
- A cause and effect relationship has not been established between the consumption of collagen hydrolysate and maintenance of joints.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on collagen hydrolysate and maintenance of joints pursuant to Article 13(5) of Regulation (EC) No 1924/2006 (Claim serial No: 0297_DE). March 2011. Submitted by Gelita AG.

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GLOSSARY / ABBREVIATIONS

dGEMRIC	delayed gadolinium enhanced MRI of cartilage
Hyp	hydroxyproline
MRI	magnetic resonance imaging
VAS	visual analogue scale